cocci except *E. faecalis*, although a few strains of staphylococci and *E. faecium* with acquired resistance contingent on efflux or acetylation of dalfopristin. Linezolid has near-universal activity against gram-positive cocci, with MICs narrowly distributed from 0.5 – 4 mg/L. Linezolid-resistance has only been encountered in a few mutants of enterococci and one MRSA, virtually all of them selected during therapy in under-dosed patients or those with indwelling devices or difficult-to-reach infections.

Agents such as linezolid give vital new options against gram-positive bacteria. Increasingly, therefore, the centre of concern must swing back to gram-negative bacteria, where pan-resistance is emerging in a few non-fermenters – mostly *P. aeruginosa* from cystic fibrosis in the West, but more widely among pseudomonads and *Acinetobacter* spp. in East Asia. Against these organisms there is a dearth of advanced antimicrobial developments although carbapenemase inhibitors, efflux inhibitors and antimicrobial peptides all provide prospects for the more distant future.

Understanding antibiotic resistance development in the immunocompromised host

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Infections with a variety of agents cause major problems in the immunocompromised host. In addition to infection control techniques, a number of strategies utilizing antimicrobial agents have been employed: therapeutic use for documented infections; preemptive use for suspected infections; and prophylactic use to prevent infection in high-risk patients. Among the major risk factors for bacterial infections in the immunocompromised host are neutropenia, breakdown in mucosal protective barriers secondary to immunosuppressive agents, and contamination of surgical procedures (especially in solid organ transplants) as well as the further immunosuppressive effects of opportunistic (especially viral) infections. It is the use of antimicrobial agents in this setting that is the major factor in selecting for resistant bacteria. In some cases, the organisms emerge because they are not included in the spectrum of activity of the drug being utilized. In other cases, antibiotic use results in the selection of resistant bacteria originally in the spectrum of the agent being utilized. Examples of this are seen in the studies in which earlier generation fluoroquinolones (which lacked outstanding coverage against Gram-positive bacteria) were used for prophylaxis in neutropenic patients; and as a result of this, the patients undergoing such prophylaxis showed a marked increase in incidence of infections due to viridans streptococci.

The addition of penicillin to the regimen initially suppressed the viridans streptococcal infections, but resulted in the emergence of penicillin-resistant viridans streptococci. Indeed, it is often possible to predict the organisms likely to emerge in the setting of extensive antimicrobial use for therapy or prophylaxis. Extensive use of expanded-spectrum cephalosporins often results in the emergence of *Enterobacter cloacae*, *Enterobacteriaceae* with extended-spectrum beta-lactamases, vancomycin-resistant enterococci, and nonfermenting organisms such as *B. cepacia*, *Acinetobacter* species, etc. The use of beta-lactam/beta-lactamase inhibitors often results in the emergence of MRSA, or *Enterobacteriaceae* with inhibitor-resistant beta-lactamases. Substituting carbapenems also selects for MRSA, *Stenotrophomonas maltophilia*, *Serratia marcescens* with carbapenemases, or vancomycin-resistant *Enterococcus faecium*. As noted before, the earlier generation fluoroquinolones often selected Gram-positive organisms, but the newer fluoroquinolones can select for MRSA, or fluoroquinolone-resistant *Enterobacteriaceae* and/or *Pseudomonas aeruginosa*. Extensive use of vancomycin or teicoplanin is responsible for the emergence of vancomycin-resistant enterococci and strains of *S. aureus* with intermediate resistance to glycopeptides (GISA). Many of these organisms are Gram-negative, but the Gram-positive bacteria have become a major problem in the immunocompromised host in recent years. Among the important Gram-positive organisms causing problems in this setting are methicillin- and fluoroquinolone-resistant *S. aureus*, methicillin-resistant coagulase-negative staphylococci, beta-lactam-resistant viridans streptococci, and vancomycin-resistant enterococci. Interestingly, three of the four of these organisms are bacteria that are usually considered to be of relatively low virulence and are part of the normal human bacterial flora. However, it is the resistance to antimicrobial agents in these organisms that makes them dangerous in the immunocompromised host.

The development of resistance to antimicrobial agents in bacteria occurs by one of two mechanisms: chromosomal mutation or dissemination of resistance genes among microorganisms. These two mechanisms of resistance have clinical significance. Emergence caused by chromosomal mutation is a rare event and is stable when it occurs. It involves a single strain, a single resistance gene and is selected for at the site of infection. It is selected by a specific antimicrobial given to a specific patient and the resistant clones can lead to therapeutic failure or disseminate through cross-infection. Antibiotic combinations may prevent the selection of resistance due to chromosomal mutation. On the other hand, resistance related to the dissemination of resistance genes among microorganisms (eg, plasmid- or transposon-mediated resistance) is a relatively frequent event and of variable stability. It involves two strains of bacteria and often involves multiple resistance determinants. Selection is frequently at a site other than that of

infection (ie, in the gut or the environment) and it may be selected for by as many antimicrobials as there are resistance determinants in a given plasmid or transposon. The resistant strains may lead to superinfection; and dissemination of the resistance may occur by spread of the resistant strain, or by spread of the resistance determinants to other bacteria. Antibiotic combinations are unlikely to prevent this type of resistance and may even enhance the selection of resistant strains. The likelihood of developing resistance during therapy depends upon the resistance mechanism and the genetic constitution of the infecting organism. Thus, acquisition of new resistance genes during therapy is quite unlikely. Mutation involving ribosomal binding sites of bacteria are selected with relatively high frequency in organisms with low copy number of ribosomal genes such as *Helicobacter pylori* and *Mycobacterium tuberculosis* and other mycobacteria. However, mutational resistance due to ribosomal binding site changes is much less likely in organisms such as staphylococci and enterococci which have a high copy number of ribosomal genes.

The *Enterococcus* is a beautiful paradigm of an organism highly equipped to survive in the antibiotic era. Enterococci are intrinsically resistant to beta-lactams and have low-level intrinsic resistance to aminoglycosides and lincosamides. They have acquired resistance to virtually every other antibiotic (including newer agents such as quinupristin/dalfopristin and even linezolid). Among the types of bacterial resistance acquired by the enterococci, none is more remarkable than its acquisition of resistance to vancomycin. In order to do this, the *Enterococcus* basically had to acquire genes that enabled it to synthesize unique cell wall precursors which would not bind vancomycin. Genes found in vancomycin-resistant enterococci are not native enterococcal genes, but likely have been acquired from a variety of cryptic anaerobes that are part of normal flora and are difficult, if not impossible to identify by current cultural techniques. Resistance to penicillin in viridans streptococci is the result of mutations in penicillin-binding proteins that decrease affinity for penicillin. The fact that viridans streptococci could develop penicillin resistance in the presence of pressure from continuous heavy use of penicillin and other beta-lactams has been known since the 1970s when penicillin-resistant strains were noted to cause endocarditis in patients receiving continuous penicillin prophylaxis to prevent recurrence of rheumatic fever. The significance of resistance in viridans streptococci is enhanced by the fact that genes or portions of genes from viridans streptococci have clearly been transferred into pneumococci and the resultant mosaic genes in pneumococci are the cause of penicillin resistance in this organism.

Resistance to methicillin in staphylococci is related to the acquisition of a gene which encodes a penicillin-binding protein (PBP2) that has markedly decreased affinity for methicillin. The genetic control of this gene is complicated. More recently, strains of *S. aureus* with intermediate levels of resistance to glycopeptides have been described. Although the exact mechanism of resistance in these strains is not known, it undoubtedly involves a series of mutations that ultimately decrease the effectiveness of penicillin-binding protein 4 and thus decrease cross linking of the cell wall. This results in uncrossed linked polymers which bind vancomycin or teicoplanin like a sponge. More recent studies have shown that virtually all of the GISA strains identified to date are of a similar *agr* type group (Group 2) and that these strains have mutations in *agr* function that alters their virulence and gives them enhanced ability to produce biofilm and adhere to foreign substances.

It is clear from the above that bacteria have a remarkable ability to develop resistance to antimicrobial agents. This leads to a continuous challenge to utilize antimicrobial agents effectively and to look for antimicrobial agents active against new targets in resistant bacteria.

Gram-positive infections and the immunocompromised host: the role of linezolid

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Cancer patients are prone to infections caused by Gram-positive cocci, in particular coagulase-negative staphylococci and viridans streptococci. This is due to the frequent long-term use of central venous catheters, severe mucosal damage from aggressive chemotherapy and the widely applied oral antimicrobial prophylaxis aimed at Gram-negative aerobic pathogens. As resistance to beta-lactam antibiotics among Gram-positive pathogens grew continuously over the past decade, clinicians relied increasingly on glycopeptides especially in neutropenic patients with malignancies—a patient population that is at increased risk for the development of resistant strains. Consequently, reports of vancomycin and teicoplanin resistance increased in both enterococci and staphylococci, making it necessary to reconsider the empiric use of glycopeptides and to evaluate new antimicrobial treatment strategies in these patients.

Linezolid is the first oxazolidinone, a new synthetic class of antimicrobials, and is highly active against Gram-positive cocci including resistant strains. In a series of multinational, comparative clinical trials linezolid has been shown to be efficacious and safe in complicated skin and soft tissue infections, nosocomial pneumonia, and bacteremia. These data suggested that linezolid may serve as a useful addition to the therapeutic armamentarium for the treatment of infections in immunocompromised patients with malignancies. First results of studies in this patient group have shown promise.

Smith et al[1] investigated the efficacy of linezolid 600 mg IV every 12 hours in 65 neutropenic patients